UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,593	10/18/2001	Nana K. Ayisi	S&B-C161	5237

30132 7590 10/21/2003

GEORGE A. LOUD
3137 MOUNT VERNON AVENUE
ALEXANDRIA, VA 22305

EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	8

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/978,593	Applicant(s) AYISI, NANA K.	
	Examiner Ulrike Winkler	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 4, 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-30* is/are pending in the application.

4a) Of the above claim(s) *23-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of Group I with further lection of HIV in Paper No. 7 is acknowledged. The traversal is on the ground(s) that it would not be a burden to search all listed viruses when searching the art for extracts of *O. gratissimum.* This is not found persuasive because the different viruses represent different families, having different pathologies and having achieved separate status in the art as evidenced by their different classification.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that claim 19 links inventions (A)-(F) the restriction requirement among the linked inventions is subject to the nonallowance of the linking claim, claim 19. Upon the allowance of the linking claim, the restriction requirement as to the linked inventions shall be withdrawn and any claim depending from or otherwise including all the limitations of the allowable linking claim will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim depending from or including all the limitations of the allowable linking claim is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Drawings

The drawings have been approved by the Draftsperson.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting HIV viral replication in Vero cells and in Molt4 clone 8 cells with an extract of *O. gratissimum*, does not reasonably provide enablement for the *O. gratissimum* extract to inhibit HIV viral replication in a mammal or in any other cell line. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include: (1) the nature of the invention, (2) the state of the prior art, (3) the presence or absence of working examples, (4) the amount or direction or guidance presented,(5) the quantity of experimentation necessary, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Characteristics of a compound's activity *in vitro* using purified or partially purified components generally differs significantly with the compound when used in a living body. There is insufficient guidance and objective evidence that such teachings would be indicative of the effect of *O. gratissimum in vivo*, i.e. in an individual; wherein it would not be predictable to one of skill in the art to use the method in order to treat HIV viral infection in any individual. Those of skill in the art recognize those *in vitro* assays and or cell-cultured based assays are generally

useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlation is generally lacking. Additionally, cultured cell lines generally differ significantly from *in vivo* animal models. The compound must be delivered into the circulation in a sufficient concentration and for a sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In addition, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy with the compound. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation or immunological activation. In addition, the composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the composition has no effect, circulation into the target area may be insufficient to carry the composition and a large enough local concentration may not be established.

The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived.

Further, although drawn specifically to cancer cells, in *in vitro* culture the cells exhibited inhibitory effects with test compounds, yet the same effect was not observed *in vivo* [see Planchon et al. Differential effect of butyrate derivatives on human breast cancer cells grown as organotypic nodules in vitro and as xenografts in vivo, In Vivo (1992) Vol. 6, pages 605-610, see abstract; Kerr et al. The relationship between cytotoxic drug exposure and tumor cell kill *in vitro* and in *vivo*, In Vivo (1991) Vol 5, pages 385-388]. In another *in vivo* vs. *in vitro* model, passaged U-937 human leukemic cells behaved differently when these cells are passage *in vitro* or *in vivo* [see Chomienne et al., Discrepancy between *in vitro* and *in vivo* passaged U-937 human leukemic Cells: Tumerorigenicity and sensitivity to differentiating drugs. In Vivo, 1988]. Passageing the U-937 cells in mice resulted in the cells losing the ability to differentiate when exposed to differentiating drugs (see Figure 6). The authors were not able to explain this dedifferentiation phenomenon for leukemic cells, but it is clear that host factors play an important role, either in selecting pre-existing less differentiated cells or by inducing modifications in the cells' proliferation/differentiation status (see p. 286, column 1, 1st paragraph). Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

In a statement made by Joanne Schellenbach, spokeswoman for the American Cancer Society, regarding a study finding [see Washington Times Article by Joyce Howard Price, November 16, 2001, p. 3] she noted that "results of animal studies cannot always be easily replicated in humans." In fact, she said, "not a large percentage" of promising results in animal studies "pan out" for use in humans.

The effect of an inhibitor is dependent on the virus, inhibitor concentration and cell line used [see Kirsi et al. Broad Spectrum antiviral cavity of 2-beta-d ribofuranosylselenzaole-carboxaimde, a new antiviral agent, Antimicrobial Agents and Chemotherapy (1983) Voll. 24, No. 3, pages 353-361]. The experiments in the study were controlled for the (i) number of times the cells were passaged (ii) the drug lot and dilution used (iii) the conditions under which the virus pool was frozen (iv) the amount of virus added to each well. The results indicate (Kirsi et al., see table 2) that the inhibitor may be effective in one cell line but not in another cell line for the same virus, in this case several different DNA and RNA viruses were tested using three different inhibitor compounds.

Furthermore, inhibiting the replication/infection of a virus *in vitro* with a compound would not provide evidence that the compound would inhibit the intact virus from infecting its target cell *in vivo*. The example of suramin, this drug was shown to be very promising in *in vitro* studies to block the infectability of HIV [see Mitsuya et al. Suramin protection of T Cells *in vitro* against infectivity and cytopathic effect of HTLV-III. Science, (1984) Vol. 226, pp.172-174.]. Further study using suramin as an anti-AIDS drug contradicted the results expected from the *in vitro* tests. Sandström et al. [Antiviral Therapy in AIDS: Clinical and pharmacological properties and therapeutic experience to date. Drugs (1987) Vol. 34, pages 372-390.] teach that *in vivo* experiments demonstrate no significant clinical or immunological improvement and the net effect of suramin was harmful. Therefore, the use of *in vitro* tests is not accepted as an indicator of *in vivo* activity.

The specification does not provide sufficient guidance for the inhibition of a HIV viral infection in a patient with a *O. gratissimum*. There is not indication that high enough

concentrations of the compound can be achieved in the patient to effect the viral replication *in vivo*. It is not a straightforward process to go from *in vitro* data to an *in vivo* treatment. Thus, the lack of working examples regarding treatment of HIV infection in a patient, the lack of guidance in the specification, and the unpredictability regarding extrapolating *in vitro* data to an *in vivo* treatment method greatly reduces the probability that one of skill in the art would successfully obtain the claimed invention without undue experimentation.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by El-Said et al. (Planta Medicine, 1969).

The instant invention reads on treatment of a viral infection *in vivo* using an extract of *Ocimum gratissimum.*

El-Said et al. disclose that use of an extract of *O. gratissimum* has been used in Nigerian herbal medicine for the treatment of fevers (see abstract). Fevers is a symptom which is

associated with viral or bacterial infections. Therefore, the treatment of viral infection using an extract of *O. gratissimum* is anticipated by El-Said et al.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 or for informal communications use 703-746-3162.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER